REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 1-13 and 29-50 are pending in the application and are under consideration, and Claims 14-28 have been withdrawn from consideration.

By the present amendment, Claim 10 is amended to delete a characterization of the polypeptide encoded by SEQ ID NO. 1394 which is unnecessary to distinguish the claimed invention from the prior art. Support for the amendment of Claim 10 may be found in the Claim as previously presented.

Claims 11-13 are canceled without prejudice or disclaimer to the subject matter disclosed therein.

Applicants reserve the right to pursue the canceled subject matter in a divisional and/or continuation application. Support for these amendments can be found at least in the claims as originally filed. These amendments are not believed to introduce any prohibited new matter.

I. Claims Allowed

Applicants thank the Examiner for indicating that claims 42 and 46 have been allowed.

II. Rejections Withdrawn

Applicants also thank the Examiner for withdrawal of the following rejections. The prior rejection of claims 1, 5, 9 and 10 under 35 U.S.C. § 112, second paragraph, has been withdrawn. The rejection of claims 1, 5 and 10 under 35 U.S.C. § 102(b) for being allegedly anticipated by Haertl et al. has been withdrawn. The rejection of claims 1, 5 and 10 under 35 U.S.C. § 102(b) for being allegedly anticipated by Matsutani et al. has been withdrawn. The

rejection of claims 1, 5 and 10 under 35 U.S.C. § 102(b) for being allegedly anticipated by Lambert-Zechovsky et al. has been withdrawn.

III. Rejections under 35 U.S.C. § 102(b)

Claims 5, 9, 29 and 50 stand rejected as allegedly anticipated by Blattner et al. (EMBL records AE000213 and AAC74219) or Oshima et al. (EMBL records D90748 and BAA35957). The rejection is respectfully traversed.

Applicants direct the Examiner's attention to the nucleotide alignments produced by BLAST at http://www.ncbi.nlm.nih.gov/BLAST/ as provided by NCBI which are attached as Exhibit A. The alignments demonstrate that the referenced DNA sequences are identical to SEQ ID NO: 1394 for **not more than 23 sequential nucleotide bases** at any point. Claims 5, 9 and 50 are directed to nucleic acid sequences **comprising more than 23 sequential nucleotide bases of SEQ ID NO: 1394**. The number of identical amino acids encoded by the nucleic acids of the invention and the reference sequences is not relevant. Neither Blattner et al. or Oshima et al. teach or suggest isolated nucleic acids comprising 25 or 30 sequential nucleic acids of SEQ ID NO: 1394. Accordingly, the references cannot anticipate the claimed invention and the rejection should be withdrawn.

Claim 29 recites an isolated nucleic acid which encodes a polypeptide comprising SEQ ID NO: 7056. Blattner et al. and Oshima et al. teach a sequence with homology to SEQ ID NO: 7096. However, neither Blattner et al. or Oshima et al. teach or suggest SEQ ID NO: 7056, nor do they teach an isolated nucleic acid sequence encoding a polypeptide comprising SEQ ID NO: 7056 and cannot anticipate the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 5, 9, 29 and 50 under 35 U.S.C. § 102(b).

IV. Rejections under 35 U.S.C. §§ 101 and 112, first paragraph

Claims 1-13, 29-41, 43-45 and 47-50 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph as allegedly not supported by either a specific, credible and substantial utility or a well established utility. By the present amendment, Claims 11-13 have been canceled

and the rejection is moot as to those claims. As to claims 1-10, 29-41, 43-45 and 47-50, the rejection is respectfully traversed.

Applicants submit that at least the nucleic acids of Claims 1, 5, 9, 10 and 50 have a well established credible, substantial, and specific utility in that the nucleic acids may be used for the detection of the *E. cloacae* pathogen as previously acknowledged for Claims 1, 5, 9, 10 by the Examiner in Paper No. 19. The Examiner has not presented a specific reason for re-applying the previously withdrawn rejection to Claims 1, 5, 9, 10.

The rejection is respectfully traversed on two further grounds. Applicants submit that a well established utility would be apparent to one of skill in the art from the disclosure of the specification for the invention as described in each claim as currently presented. Applicants further submit that a specific, credible and substantial utility is asserted in the specification for the invention as described in each claim currently presented.

Applicants believe that the Examiner has misinterpreted some of the evidence submitted in the Amendment and Reply submitted on June 22, 2001. Therefore, Applicants intend the following comments to clarify the evidence presented therein in addition to presenting further evidence in support of the utility of the claimed invention.

A. The claimed sequences have a well established utility.

Turning firstly to evidence which demonstrates a well established utility for the nucleic acid sequence (SEQ ID NO: 1394) and the polypeptide which it encodes (SEQ ID NO: 7056), a "well established utility" is a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. See the *Revised Interim Utility Guidelines Training Materials* of the U.S.P.T.O. at page 7. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record. See, *Utility Examination Guidelines*, 66 FR 1092 (Jan. 5, 2001).

Applicants submit herewith an article by Douglas R. Smith (1996, Trends in Biotechnology, 14:290-3), attached as Exhibit B. Smith illustrates the understanding of one

of skill in the art at the time preceding the priority date of the application regarding the identification of useful target reagents for antimicrobial development. Smith teaches that one of skill in the art seeks to identify essential genes and that the sequences and proteins encoded by those essential genes are useful in various methods for antimicrobial development. Such essential sequence and the proteins encoded by those sequences are useful in such methods, for example, as probes, primers, research reagents (drug screening targets) and tools.

Figure 1 of Smith at page 291 provides a sketch of the steps taken by one of skill in the art in determining that a microbial gene and the polypeptide which it encodes perform essential functions and is therefore a useful reagent in therapeutics development. In Figure 1, two paths are shown. To the left, genes with homologs which have recognizable functions are identified. To the right, genes which are not identified by homology may be identified by motif analysis.

Taking the path through homology identification first, Table 2 of the present specification informs one of skill in the art that nucleic acid SEQ ID NO: 1394 encoding polypeptide SEQ ID NO: 7056 has a high homology to the ymfc gene (b1135) of *E. coli*. Of course, one of skill in the art would have made the same determination given the disclosure of only SEQ ID NO: 1394 by routine reference to research databases as described by Smith on pages 291-2 or the instant specification at pages 48-49. Smith indicates that sequence homology was the most powerful tool at the time for identifying the function of genes and gene products.

The SWISSPROT entry for ymfc (b1135) has Accession No. P75966 (NCBI entry gi:2501525) and was created November 1, 1997. A copy of the NCBI entry was attached as an exhibit to Applicants' Amendment and Reply of June 22, 2001. From this homology identification, one of skill in the art would have immediately appreciated that SEQ ID NO: 1394 encoding polypeptide SEQ ID NO: 7056 was a member of the rsuA family of pseudouridine synthase. One of skill in the art would also know that pseudouridine synthase was believed to be an essential protein. For a discussion of the well established essentiality of the pseudouridine synthase which precedes the priority date of the present application see,

for example, Koonin (1996, Nucleic Acids Research, 24:2411-15) which was submitted with Applicants' Amendment and Reply of June 22, 2001.

Applicants note that the Examiner has mistakenly interpreted the "[WARNING]" comment of the NCBI entry to indicate that the functional identification is dated November 23, 1998. However, this comment only indicates that entry gi:2501525 was replaced with a newer entry gi:3916025 on that date. The exhibit submitted by Applicants is the prior entry apparently dating from November 1, 1997. An unidentified portion of the annotation may have been updated on July 15, 1998. However, both the creation of entry gi:2501525 and the unidentified update precedes the filing date of the present application.

Smith teaches that genes may be identified by motif analysis if one is not convinced of the utility of SEQ ID NO: 1394 encoding polypeptide SEQ ID NO: 7056 by the homology based functional determination. Smith teaches the use of the PROSITE motif database, among others, for gene function assignment. NCBI entry gi:2501525 (the SWISSPROT entry for ymfc (b1135)) contains a cross reference to PROSITE entry PS01149. Of course, one of skill in the art could have easily located the PROSITE entry using routine database references described by Smith on page 292. PROSITE entry PS01149 and its corresponding documentation was provided to the Examiner as an exhibit to Applicants' Amendment and Reply of June 22, 2001. The pattern was created in November 1995, prior to the priority date of the present application. On page 11 of Applicants' Amendment and Reply of June 22, 2001, the occurrences of the PROSITE pattern for rsuA pseudouridine synthase is shown for residues 78-93 of SEQ ID NO: 7056.

Applicants note that the Examiner appears to have misread the pattern shown in PROSITE entry PS01149. The Examiner seems to read the pattern as limited to the four residue sequence Gly-Arg-Leu-Asp (GRLD). The Examiner refers to a protein with these four residues having a different function to imply that identification by PROSITE motif is not credible. However, the pattern is actually much more specific than just GRLD. The pattern is Gly-Arg-Leu-Asp-Xxx-Xxx-(Ser, Thr or Ala)-Xxx-Gly-(Leu, Ile, Val, Phe or Ala)-(Leu, Ile, Val, Met or Phe)-(Leu, Ile, Val, Met or Phe)-(Leu, Ile, Val, Met or Phe)-(Ser or Thr)-(Asp, Asn, Ser or Thr); where Xxx is any residue and parentheses indicate alternative

residues at that site. The NR lines of the PROSITE entry indicate that all 18 sequences now known to belong to the rsuA class of pseudouridinie synthase are identified by this pattern and no false positives are found in SWISSPROT.

One of skill in the art at the priority date of the present application would arrive at the same functional identification by reference to the teaching of Koonin (1996, Nucleic Acids Research, 24:2411-15, submitted with Applicants' Amendment and Reply of June 22, 2001). Koonin teaches that pseudouridinie synthases have certain signature motifs beyond the PROSITE motif. All three signature motifs taught by Koonin are found in the polypeptide SEQ ID NO: 7056 encoded by SEQ ID 1394 as shown on page 11 of Applicants' Amendment and Reply of June 22, 2001. The teaching of Koonin presents motif identifiers with details which complement and expand on the PROSITE entries. Koonin also teaches that pseudouridinie synthases perform essential functions.

The Examiner has apparently misinterpreted the purpose of the submission of Koonin. Relevant to the present discussion, Koonin establishes the fact that one of skill in the art would immediately recognize that the nucleic acid sequence and polypeptide of SEQ ID NOs: 1394 and 7056 were an essential gene and gene product. The sequences of the invention are shown to have had a well established utility at the time of the invention because Koonin teaches both the means of identification and the essential nature of the presently elected sequences of the invention.

Once identified as an essential gene, either by homology or motif analysis, Smith describes a number of well established utilities for the nucleic acid sequence, probes and primers derived therefrom, the protein encoded by the gene, and methods and materials for making such a protein as research tools and reagents for antimicrobial development. Similar examples of various utilities are given throughout the present specification.

Based on the disclosure of the sequences of the invention, supported by the extensive teachings of the specification relating to the use of such sequences and their polypeptide products taken with the teachings of Smith in view of the knowledge of one of skill in the art exemplified by the databases and the teachings of Koonin, one of skill in the art would immediately appreciate that the embodiments of the invention described in the claims have a

well established utility. Therefore, the requirements of 35 U.S.C. § 101 are met because the claimed invention has a well established utility and one of skill in the art would therefore know how to use the invention in accordance with 35 U.S.C. § 112, first paragraph.

B. The disclosure asserts a credible, specific and substantial utility.

With regard to the assertion of a credible and substantial utility in the specifications which was described in Applicants' Amendment and Reply of June 22, 2001, the Examiner has raised various objections to Applicants presentation. The Examiner has requested that Applicants point to the section of the instant specification that defines the claimed nucleic acid as encoding a polypeptide with pseudouridine synthase biological activity. Applicants respectfully submit that a sufficient explication of the identification of the SEQ ID NOs: 1394 and 7056 as a pseudouridine synthase as shown through its disclosed homology with the ymfc gene of *E. coli* was discussed in detail in Applicants' Amendment and Reply of June 22, 2001. Therein, Applicants directed the Examiner's attention to the description of Table 2 of the specification at pages 37-39 and to the entry in Table 2 which identifies the homology to the ymfc gene of *E. coli*. The specification teaches that such an identification may be used for the determination of a function at page 53. Public database entries, available at the time the invention was filed, for the ymfc gene of *E. coli* provide complementary and confirmatory information which has been shown to be supported by multiple contemporaneous sources. Applicants submit that the teachings of the specification, taken as a whole, constitute a credible functional identification.

The Examiner has taken the position that the functional identification of polypeptide SEQ ID NO: 7056 encoded by SEQ ID 1394 in Table 2 of the specification is identified at page 53, line 7 as "putative." The Examiner is reminded that the definition of putative is (1) commonly accepted or supposed, (2) assumed to exist or to have existed. (See, for example, Merriam-Webster Collegiate Dictionary Online http://www.m-w.com/home.htm) Therefore, unless presented with a reason to doubt the identification, it should be taken as commonly accepted. The applicable standard is a credible utility and not a proven or certain utility. See,

Utility Examination Guidelines, 66 FR 1092 (Jan. 5, 2001). The training manuals describe how this standard is to be applied as follows:

> Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. See the *Revised Interim Utility Guidelines Training Materials* of the U.S.P.T.O. at page 5.

The Examiner has not shown that either the logic underlying Applicants' assertion of utility is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

Furthermore, the utilities which are disclosed are specific and substantial. A few examples of specific utilities may be found for example on pages 79-85 of the specification. Several of the asserted utilities relate to the use of the nucleic acids and polypeptides of the invention as probes, research tools, and reagents for the development of antibacterial agents. "Substantial utility" is defined in the training materials of the U.S. Patent and Trademark Office as:

> a utility that defines a "real world" use. For example, . . . an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. See the *Revised Interim Utility Guidelines Training Materials* of the U.S.P.T.O. at page 6.

As set forth above the credibility and substantiality of the identification given in Table 2 may be supplemented and confirmed by reference to several independent contemporary sources. The Examiner notes that Koonin does not mention *E. cloacae* at all. This is not a surprise. The present invention provides the first disclosure of the rsuA pseudouridine synthase of *E. cloacae.* Koonin is submitted in support of the fact that the identification of SEQ ID NOs: 1394 and 7056 as homologous to the ymfc gene (b1135) of *E. coli* established a substantial and credible utility for the claimed invention at the time of the invention. Koonin clearly shows that one of skill in the art would regard the identification of SEQ ID NOs: 1394 and 7056 as a pseudouridine synthase as credible. Even if ymfc of *E. coli* is

labeled as a hypothetical protein, its homology with the rsuA class of pseudouridine synthase is substantial and the functional identification is well supported and cross referenced to independent sources such as PROSITE and Koonin. Contrary to the Examiner's assertion, SWISSPROT Accession No. P75966 (NCBI entry gi:2501525), the entry for ymfc (b1135), was created November 1, 1997. Its comment section does not indicate that it was created in November of 1998, rather the entire entry was superceded by a new entry with a new "gi:" number at that time. The "[WARNING]" comment merely serves to inform one that the entry is out of date.

Therefore, the specific and substantial asserted utilities of the instant specification are credible because the functional identification of the claimed sequences is credible and the requirements of 35 U.S.C. § 101 are met and one of skill in the art would therefore have known how to use the invention in accordance with 35 U.S.C. § 112, first paragraph.

For at least the forgoing reasons, the withdrawal of the rejection of Claims 1-13, 29-41, 43-45, 47-50 under 35 U.S.C. §§ 101 and 112, first paragraph is respectfully requested.

V. Rejections under 35 U.S.C. § 112, first paragraph

A. Claims 11-13 stand rejected under 35 U.S.C. § 112, first paragraph, because the disclosure allegedly does not enable any person skilled in the art to which it pertains to use the invention commensurate with the scope of the claims. Without acceding to the Examiner's arguments, Applicants have canceled Claims 11-13, thereby mooting the rejection. Applicants reserve the right to file a divisional or continuation application directed to the canceled subject matter.

B. Claims 29, 33, 37-38 stand rejected under 35 U.S.C. § 112, first paragraph, because the disclosure allegedly does not provide enablement for the use of any nucleic acid that shares 70% sequence identity with SEQ ID NO 1394. The rejection is respectfully traversed. Claims 29, 33, 37-38 recite an isolated nucleic acid sequence encoding a polypeptide which comprises SEQ ID NO: 7056 or a variant thereof. Such a nucleic acid sequence may be used for example for the expression of a polypeptide which comprises SEQ

ID NO: 7056 as described in the specification beginning at page 50 and as is well known in the art. Furthermore, the expressed protein may be used in drug screening assays such as are described in the specification, for example, at pages 79-81. Applicants submit that the specification is fully enabling for these and other uses of the claimed nucleic acid sequences.

VI. Rejections under 35 U.S.C. § 112, second paragraph

Claims 10 and 37-38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for its recitation of a biologically active polypeptide of *E. cloacae.*

With regard to Claim 10, the Examiner inquires as to nature of the biological activity claimed. Applicants submit that one of skill in the art would understand the metes and bounds of the term "a biologically active polypeptide of *E. cloacae.*"

However, simply in order to expedite prosecution of the application, Claim 10 has been amended to delete to characterization of the polypeptide encoded by SEQ ID 1394. Claim 10, as amended, recites an isolated nucleic acid comprising a nucleotide sequence of at least 30 consecutive nucleotides in length, wherein the sequence can hybridize under conditions of high stringency to a nucleic acid comprising SEQ ID NO: 1394 wherein said nucleic acid is not immediately contiguous with both of the coding sequences with which SEQ ID NO: 1394 is immediately contiguous in the naturally-occurring *E. cloacae* genome. The biological activity of the sequence encoded by SEQ ID NO: 1394 is immaterial to defining the metes and bounds of the claimed isolated nucleic acid.

With regard to Claims 37 and 38, the Examiner asserts that the invention is not distinctly claimed without providing a clear reason for the rejection.. The Examiner inquires as to the size of the nucleic acid and the function of the polypeptide. Applicants submit that the size of the nucleic acid is clearly indicated as being at least long enough to encode a polypeptide with 90% (Claim 37) or 95% (Claim 38) sequence identity to SEQ ID NO: 7056. One of skill in the art would understand that the smallest possible size for the claimed nucleic acids may be calculated by taking the length of SEQ ID NO: 7056 multiplied by 3 x 0.9 for Claim 37 or 3 x 0.95 for Claim 38. One of skill in the art would further understand that the term "comprising" indicates that the claimed isolated nucleic acid may include further

sequences. Such sequence may include sequence elements such as are used for replication of the sequence, restriction sites, operators, promoters, tag encoding sequences, and the like.

As to the biological function of the polypeptide encoded by the claimed nucleic acid sequences, Applicants submit that under 35 U.S.C. § 112, second paragraph, a function of a compound need not be recited in a claim for it to be definite. The claimed nucleic acid sequence is particulary pointed out and distinctly claimed so that one of skill in the art will know the metes and bounds of the claimed invention. The requirements of 35 U.S.C. § 112, second paragraph are believed to be fully met by Claims 37 and 38 as presented.

For at least the forgoing reasons, Applicants respectfully request withdrawal of the rejection of Claims 10, 37-38 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: March 25, 2002

Attachment to Amendment and Reply Dated March 25, 2002
Marked up Claim 10

10. (Thrice Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 30 consecutive nucleotides in length, wherein the sequence can hybridize under conditions of high stringency to a nucleic acid comprising SEQ ID NO: 1394,[which encodes a biologically active polypeptide of *E. cloacae*, and] wherein said nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.